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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	11

DATE MAILED: 08/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/899,440	STEIN, CY	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-20 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9-20 and 28* is/are rejected.

7)☒ Claim(s) *7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application/Amendment/Claims

1. Applicant's response filed June 16, 2003 has been considered. Rejections and/or objections not reiterated from the previous office action mailed March 11, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on June 16 was filed after the mailing date of the first Office action on the merits mailed August 27, 2002. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Response to Arguments

4. Claims 17-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of heparanase expression *in vitro*, does not reasonably provide enablement for pharmaceutical compositions encompassing antisense-mediated inhibition activity of heparanase expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

make and/or use the invention commensurate in scope with these claims, and is repeated for the reasons of record set forth in the Office action mailed August 27, 2002.

Applicants have amended claim 15 to limit the instant method to *in vitro* applicability, and canceled claims 21-27 drawn to treatment utilizing the instantly claimed oligos. However, applicants have not addressed the rejection as it pertains to claims 17-20. As stated in the Office action mailed March 11, 2003, claims 17-20 have been rejected under both 35 U.S.C. § 112 1st paragraph enablement and under 35 U.S.C. § 103(a). This position, although at first glance appearing incongruous, is nevertheless consistent because the language of claims 17-20 is specifically drawn to a pharmaceutical use of the instantly claimed compound, which must be considered for compliance with 35 U.S.C. § 112 1st paragraph enablement due to the implication for *in vivo* applicability. However the intended use limitations (i.e. pharmaceutical) for claimed compositions rarely breathe life and meaning into a compound claim, and thus rarely provide patentable distinction in the consideration of prior art. In summary, the compound aspect of the claims drawn to a pharmaceutical compound may be rejected under 35 U.S.C. § 102 or § 35 U.S.C. § 103(a), while language drawn to the pharmaceutical use of such compounds may elicit a rejection under 35 U.S.C. § 112 1st paragraph enablement if the intended use is not considered to be supported by the specification. Such is the present case. The rejection of the above claims is thus maintained under 35 U.S.C. § 112 1st paragraph enablement for reasons of record.

5. Claims 1-6, 9-15, 17-20, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kussie et al., in view of Pecker et al., Froehler et al., Taylor et al., and Baracchini et al. (all of record).

Applicants have traversed the rejection of the above claims by asserting that the combination of references does not teach the claimed invention. Specifically, applicants assert that Kussie et al. does not teach SEQ ID NO: 18, and indicate that the amino acid residue 14 of Kussie et al. is different from that of the instant SEQ ID NO: 18.

This is not considered convincing, because the two transcripts are over 99% identical (see enclosed alignment). Furthermore, both are disclosed as human heparanase mRNA transcripts. Accordingly, in light of applicants' broad claim that encompasses any oligo that hybridizes and inhibits SEQ ID NO: 18, and since the reference of Kussie et al. teaches a heparanase sequence that possesses over 99 % percent identity with SEQ ID NO: 18, one of ordinary skill in the art would understand that, with very few exceptions, the vast majority of oligos that hybridize with and inhibit the human heparanase transcript of Kussie et al. would also hybridize and inhibit the human heparanase transcript of SEQ ID NO: 18. Motivation to inhibit the human heparanase mRNA transcript of Kussie et al. has been previously set forth, and is considered to also apply to the human heparanase mRNA transcript of SEQ ID NO: 18, since the reported function is identical, and the sequences are over 99% identical. The fact that Kussie et al. differs over less than 1% of the nucleotide sequence over the entire length of the transcript is not considered to invalidate Kussie as a reference in the instant rejection.

Applicants also argue that the reference of Taylor et al. merely provides a general teaching of how to obtain an active antisense molecule, but does not provide sufficient supporting details regarding how to find said active antisense molecules. Applicants assert that Taylor's reference to a bioinformatics program that assists in screening for active oligos depends upon unpublished data and is therefore not enabling.

This is not considered convincing, because applicants have not met the evidentiary standard of demonstrating that the reference of Taylor et al. is not enabled. As per M.P.E.P. § 2121:

> When the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). See also MPEP § 716.07.

Applicants have merely asserted that the reference of Taylor et al. does not provide specific information regarding how to find active antisense oligomers. To the contrary, Taylor et al. describes how antisense oligos are designed from the complement of the target sequence and targeted to desirable regions within the mRNA, the desirability of modifying such oligos to enhance their degradation and binding affinity including the use of chimeric oligos containing both DNA and RNA, and finally indicates that by using high affinity chimeras and a bioinformatics program to select accessible sites, that researchers are able to screen only 3-6 oligomers to find one that is capable of inhibiting with 66-95% efficacy. While applicants argue that this data is unpublished, it is maintained that such chimeras and bioinformatics programs are easily available to one of ordinary skill in the art, and do not constitute an issue of enablement. Even if this weren't the case, Taylor goes on to state that this combination merely reduces the time necessary to screen for active oligos, strongly implying that even without these, one can still screen for active oligos, but that it just might take somewhat longer. One of ordinary skill would still have a reasonable expectation of success in making and using such oligos. For example, see any of the five references cited in the enablement rejection that demonstrate that finding oligos that exhibit *in vitro* efficacy is routine to one of ordinary skill in the art. It is emphasized that Taylor et al. is teaching what one of ordinary skill in the art would already know, namely that

screening for active oligos that provide a high level of inhibition *in vitro* is within the grasp of one of ordinary skill in the art. As per M.P.E.P. § 2112:

> When a prior art reference merely discloses the structure of the claimed compound, evidence showing that attempts to prepare that compound were unsuccessful before the date of invention will be adequate to show inoperability. In re Wiggins, 488 F.2d 538, 179 USPQ 421 (CCPA 1971). However, the fact that an author of a publication did not attempt to make the compound disclosed, without more, will not overcome a rejection based on that publication. In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985) (In this case, the examiner had made a rejection under 35 U.S.C. 102(b) over a publication, which disclosed the claimed compound, in combination with two patents teaching a general process of making the particular class of compounds. The applicant submitted an affidavit stating that the authors of the publication had not actually synthesized the compound. **The court held that the fact that the publication's author did not synthesize the disclosed compound was immaterial to the question of reference operability. The patents were evidence that synthesis methods were well known.** The court distinguished Wiggins, in which a very similar rejection was reversed. In Wiggins, attempts to make the compounds using the prior art methods were all unsuccessful.). (Emphasis supplied).

The reference of Taylor et al. does not need to supply examples describing concentrations of reagents and incubation times to be used, because the art of *in vitro* use of antisense oligos is considered to be well developed, and is therefore considered enabled.

However, even if Taylor et al. were not enabling in terms of supplying the level of detail required for enablement, which it is, applicant is referred to the reference of Baracchini et al., cited in the instant rejection, who supplies numerous examples of exactly how to synthesize oligonucleotides, how to administer said oligos to cells *in vitro*, and how to screen such cells for inhibition, complete with all reagents, incubation times and temperatures, and further indicates the manufacturers of basic supplies required. Therefore, the references provided are considered to teach to any requisite level of detail necessary to practice applicants' invention as claimed, and the rejection is thus maintained.

Allowable Subject Matter

Claim 7 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. A sequence search performed against the oligonucleotides of SEQ ID NOS: 3, 4, and 5 indicated no anticipating prior art. Thus the oligos of the independent SEQ ID NOS recited in claim 7 are considered free of the art if rewritten in independent form and including all of the limitations of claim 1.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
August 20, 2003

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600